REMARKS

Status of the claims

Claims 1-3, 10-13, 18-25, 28-41, 46-53, 62-83, and 86-102 are pending. By the instant amendment, claim 49 is cancelled, and claims 41, 51-53 and 102 are amended to correct their dependency. In addition, claims 51-53 are amended to indicate that the glidant is optionally present in the claimed composition. No new matter is added by these amendments.

Rejection of claims 1-3, 10-13, 18-25, 28-41, 46-53, 62-83, and 86-102 under 35 U.S.C. §103(a)

Mizumoto in view of Talley

Reconsideration is respectfully requested of the rejection of claims 1-3, 10-13, 18-21, 23-25, 28-41, 46-49, 51-53, 62-83, 86-93, and 96-102 as unpatentable over Mizumoto in view of Talley.

Claim 49 has been cancelled, rendering moot its rejection under §103(a).

Claim 1 is directed to a process for preparing an oral fast-melt pharmaceutical composition. The claimed process comprises (a) a step of wet granulating a drug in an amount of about 15% to about 75% by weight of the composition together with a liquid binding agent comprising a saccharide having high moldability; (b) a step of blending with the drug a saccharide having low moldability; and (c) a step for inhibiting agglomeration of the drug. Claim 1 specifies that steps (a), (b), and (c) may occur in any order or simultaneously to result in formation of granules; that the drug has at least one property conferring upon the drug a tendency to agglomerate in the composition; and that the drug is celecoxib. Claims 2, 3, 10-13, 18-21, 23-25, 28-41, 51-53, 90-93, 97, and 98 depend from claim 1.

Similarly, claim 99 is directed to an oral fast-melt composition comprising (a) a drug in an amount of about 15% to about 75% by weight of the composition; (b) a liquid binding agent comprising a saccharide having high moldability; and (c) a means for inhibiting agglomeration of the drug; wherein the drug is uniformly dispersed in the liquid binding agent, wherein the drug has at least one property conferring upon the drug a tendency to agglomerate, and wherein the drug is celecoxib. Claims 46-48, 62-83, 86-89, 96, and 100-102 depend from claim 99.

As described in the specification, (the Examiner's attention is respectfully directed to page 9, lines 7-18), the "step for inhibiting agglomeration" required in claims 1 and 99 is "any measure taken during production of the fast-melt composition to prevent or reduce drug agglomeration or to facilitate separation of existing drug agglomerates." A means to inhibit agglomeration in fluid bed granulation, for example, may include addition of a wetting agent. Alternative or additional means to inhibit agglomeration during granulation can include, for example, pre-wetting the powder material to be granulated, such as by employing an additional, external processor with spraying capacity, and/or using an air distributor plate adapted to increase air flow along the periphery of the granulation bowl.

Talley describes substituted pyrazolyl benzenesulfonamides for the treatment of inflammation. Numerous such compounds are disclosed, including celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (see Example 2, col. 40).

Mizumoto describes, *inter alia*, intrabuccally dissolving compressed moldings comprising granules comprising a saccharide having low moldability and a saccharide having high moldability. These moldings may further comprise an active ingredient, i.e., a drug. Mizumoto describes at least forty different kinds of drugs that the moldings may comprise: antacids, serotonin $5HT_3$ receptor

antagonists, NSAIDs, steroidal anti-inflammatory drugs, antipsychotics, hypnotics, antiepileptics, antiparkinsonism drugs, antiemetics, hormone drugs, analgesics, sulfa drugs, coronary vasodilators, H_2 receptor antagonists, antiarrhythmics, cardiotonics, calcium antagonists, antihistamines, antibiotics, antitumor drugs, antidiabetics, gout-treating drugs, antiallergics, antihypertensives, central nervous system acting drugs, potassium channel activators, skeletal muscle relaxants, antispasmodics, antihyperlipemics, bronchodilators, α-andrenergic receptor blockers, blood sugar lowering drugs, digestive tract motility improving drugs, antigastritis and antigastric ulcer drugs, osteoporosis treating drugs, prostatonegaly treating drugs, expectorants, allergic rhinitis treating drugs, asthma treating drugs, and animal drugs. Please see col. 7, line 62 through col. 9, line 43. Also disclosed are peptides, polypeptides, proteins, and derivatives thereof that may be used as an active ingredient, please see col. 9, line 44 through col. 10, line 14. As discussed at col. 10, lines 15-16, preferable active ingredients include famotidine (an H_2 receptor antagonist, see col. 8, line 47), tamsulosin hydrochloride (an α-andrenergic receptor blockers, see col. 9, lines 25-26), and YM934 (a potassium channel activator, see col. 9, line 14). In the examples are also described tablets comprising acetaminophen (Example 16) and salmon calcitonin (Example 19). However, the cited art does not teach or suggest celecoxib in conjunction with a step for inhibiting agglomeration.

As disclosed in the instant application, celecoxib particles have a tendency to agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib. See page 5, lines 10-18. Because of this property, prior to the advent of the present invention, celecoxib has been unsuitable for a fast-melt formulation. Applicants have discovered that a drug having a tendency to agglomerate, such as celecoxib, which would otherwise be unsuitable

for a fast-melt formulation may nevertheless be formulated in a fast-melt formulation if a step for inhibiting agglomeration of the drug is included in the process for preparing the formulation. This is the patentable advancement of the claimed invention over the cited art.

The Office asserts that a "COX-2 inhibitor is a well-known analgesic agent, particularly, anti-inflammatory, which can be used in conjunction with other analgesic agents" and that "it would have been obvious for one of ordinary skill in the art to prepare the quick-dissolved formulation of Mizumoto using the COX-2 inhibitor, such as celecoxib in view of the teachings of Talley, because the references teach the advantageous results in the use of a well-known anti-inflammatory agent." It is well-established that obviousness can be demonstrated by combining or modifying the teachings of the prior art to produce the claimed invention only where a suggestion or motivation to do so is found either in the prior art itself or in the knowledge generally available to one of ordinary skill in the art. However, as discussed above, celecoxib particles have a tendency to agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib, and that because of this property, celecoxib has been unsuitable for a fast-melt formulation prior to the advent of the present invention. The step of inhibiting this agglomeration in the process of preparing a fast-melt composition of celecoxib is not taught or suggested in the cited art.

The Office asserts that "[t]he prior art provides the step for inhibiting agglomeration. The step is provided when the prior art adding [sic] wetting agent." Applicants respectfully disagree. As noted above, the "step for inhibiting agglomeration" required in claims 1 and 99 is "any measure taken during production of the fast-melt composition to prevent or reduce drug agglomeration or to facilitate separation of existing drug agglomerates." A means to

inhibit agglomeration in fluid bed granulation, for example, may include addition of a wetting agent. Alternative or additional means to inhibit agglomeration during granulation can include, for example, pre-wetting the powder material to be granulated, such as by employing an additional, external processor with spraying capacity, and/or using an air distributor plate adapted to increase air flow along the periphery of the granulation bowl. Nowhere does Talley describe the addition of a wetting agent to a formulation comprising celecoxib. Mizumoto mentions that various additive agents may be added to their moldings; these agents include for example, disintegrating agents, binding agents, souring agents, vesicants, artificial sweeteners, perfumes, lubricants, and coloring agents, see col. 13, lines 32-38. Thus, the cited art does not teach or suggest the use of a wetting agent with celecoxib.

Neither Mizumoto nor Talley, taken singly or together, describe every element of the process of claims 1 and 99, or the claims that depend from them, and thus the Office has failed to set forth a *prima facie* case of obviousness.

Mizumoto and Talley in view of Jain

Reconsideration is respectfully requested of the rejection of claims 1, 22, 42, 45, 50, 94, and 95 as unpatentable over Mizumoto and Talley in view of Jain.

Claims 42 and 45 were previously cancelled, and thus their rejection under §103(a) is moot. Claims 22, 94, and 95 depend from claim 1. Claim 50 depends from claim 99.

Mizumoto and Talley have been described above. Jain does not supply the deficiencies of these references. Jain describes rapidly disintegrating or dissolving solid dose formulations of nanoparticulate compositions comprising a poorly soluble nanoparticulate drug or other agent having an effective average particle size of less than about 2000 nm and a surface stabilizer adsorbed on the surface thereon. As described by Jain, the "surface stabilizer is absorbed on the surface of the active agent in an

amount sufficient to maintain an effective average particle size of less than about 2000 nm for the active agent." See col. 7, lines 21-24.

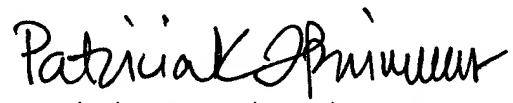
The Office asserts that "it would have been *prima facie* obvious for one of ordinary skill in the art to use the sodium lauryl sulfate and silicon dioxide in view of the teaching of Jain to prepare the quick-dissolved formulation of Mizumoto since sodium lauryl sulfate and silicon dioxide are well known tabletting aids." However, the Office has failed to explain why one skilled in the art would have been motivated to combine the references in this way, and thus has **not** shown that claims 1, 22, 42, 45, 50, 94, and 95 are *prima facie* obvious.

Nothing in Jain suggests the need for formulating their poorly soluble drug and surface stabilizer with the saccharide having low moldability and the saccharide having high moldability required by Mizumoto. At the very most, the formulations described by Mizumoto and Jain would be seen as **alternatives** to one another, which one skilled in the art would have no reason or motivation to combine. As such, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

For the foregoing reasons, the Applicants submit that the present invention is now in condition for allowance. Early allowance of all pending claims is respectfully solicited.

Respectfully submitted,



Patricia K. Fitzsimmons
Registration No. 52,849

Pharmacia Corporation
Post Office Box 1027
St. Louis, MO 63006
Telephone: 314.274.1490
Facsimile: 314.274.9095